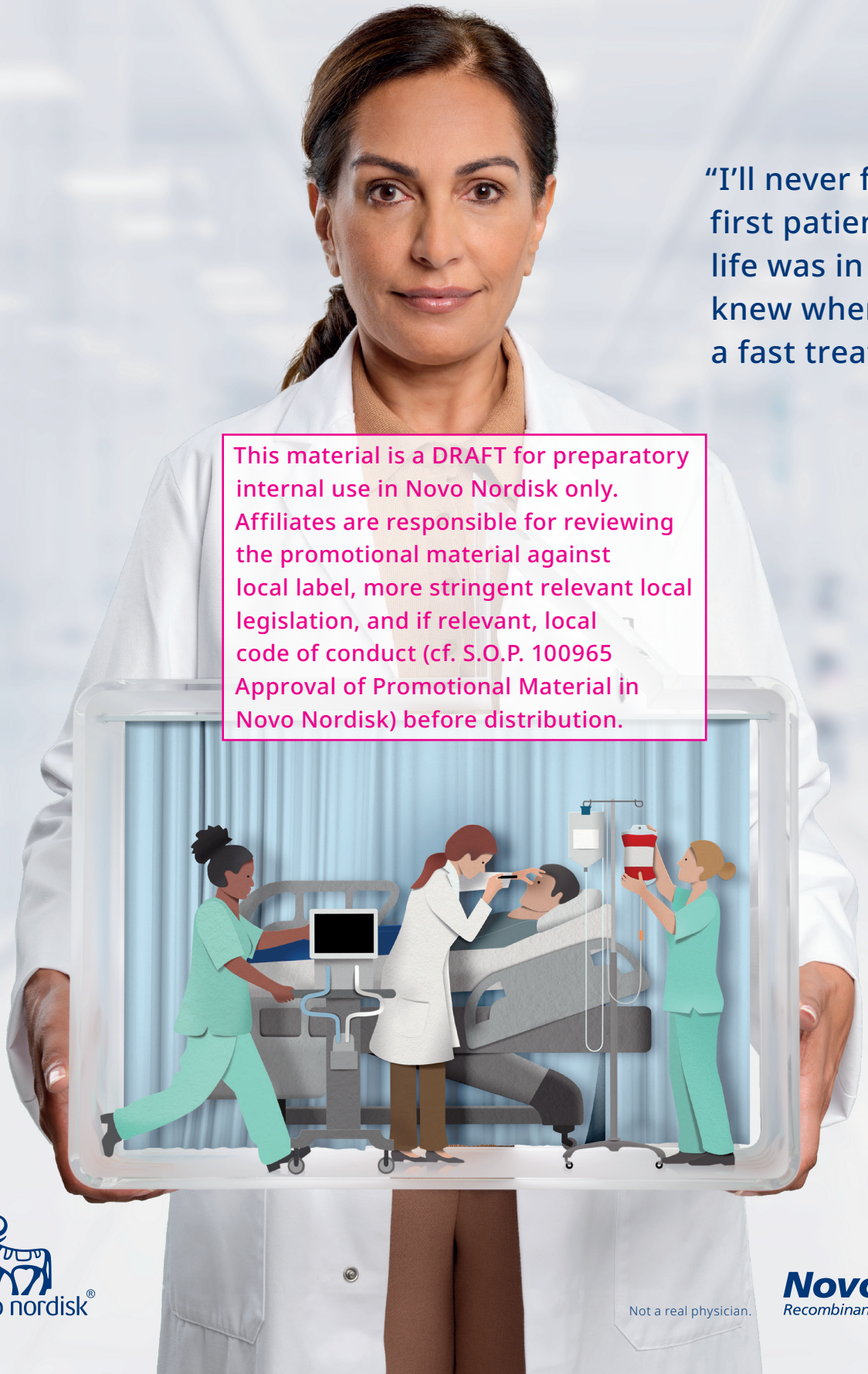
Do you remember your first NovoSeven® success story?



"I'll never forget my first patient. When his life was in danger, I knew where to turn for a fast treatment." [1,2]

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Not a real physician.

novo nordisk®

NovoSeven®
Recombinant Factor VIIa

Emergency bleeds happen

Congenital Haemophilia with Inhibitors (CHwI)

In the 1990s, the mortality for patients with congenital haemophilia A or B who develop inhibitors, regardless of severity, had dropped by half versus the 1970's ($P<0.001$). The development of inhibitors was no longer associated with increased mortality in severe haemophilia, as the mortality rates in patients with inhibitors decreased to the level seen in patients without inhibitors.[3]

The longer a bleed remains untreated, the more cumulative damage is done. CHwI patients know to treat as early as possible upon recognising a bleed.[4,5]

Patients with CHwI will seek treatment primarily at Haemophilia Treatment Centres (HTCs) but may choose the nearest emergency room if they do not know/have access to a HTC, or in an emergency if: [6,7]

They cannot access a vein

They have run out of medicine

They need emergency surgery (e.g. appendectomy) **or have suffered an acute trauma** (e.g. an accident)

Treat fast with NovoSeven®

Efficacy:

96.5% efficacy when treated within 1 hour of bleed onset*†[8]

Safety profile:

A pure rFVIIa that does not contain FVIII or FIX and works only at the site of vascular injury[1,9–12]

Speed:

Low infusion volume results in rapid preparation and administration[1,2]

Convenience:

Practical in-hospital storage and easy portability for out-patients‡[1]

Reliability:

30 years of research and clinical experience across more indications than any other agent[1,3,13–15]

* The SMART-7™ study was a prospective, observational, single-arm, multi-centre, multi-national study investigating the safety and effectiveness of room-temperature-stable NovoSeven® in people with haemophilia A or B with inhibitors in a real-world setting. The primary objective was to monitor reduced therapeutic response and neutralising antibodies to rFVIIa.[8]

† Post-hoc sub-analysis of SMART-7™ assessed haemostatic response to NovoSeven® in a real-world setting where time to first treatment was under 1 hour: a total of 318/618 bleeding episodes treated with rFVIIa monotherapy and with (1) valid efficacy assessment, (2) no missing time for bleed start, (3) no missing time for any dose administration, and (4) valid time to first treatment were included in the analysis. Effective = patient reported that the bleed "stopped"; Partially effective = patient reported that the bleed "slowed"; Ineffective = patient reported that the bleed "worsened/no change".[8]

‡ In a room temperature environment of 25 °C.[1]

Is your hospital ready for a changing landscape?

New non-factor prophylaxis options for CHwI (e.g. emicizumab) have arrived:

- It has a much longer half-life than the bypassing agents (BPAs), allowing it to remain in the bloodstream at therapeutic levels for a longer period of time ($T_{½}$=26.7 days vs.$T_{½}$=<1 day)[15]
- Patients still use BPAs to treat bleeds while taking emicizumab (75 of 104 patients required the use of a BPA in the HAVEN1 study)[5,16]

NovoSeven® (rFVIIa) is the only BPA recommended for the first line treatment of emergency bleeds for patients on emicizumab prophylaxis[5]

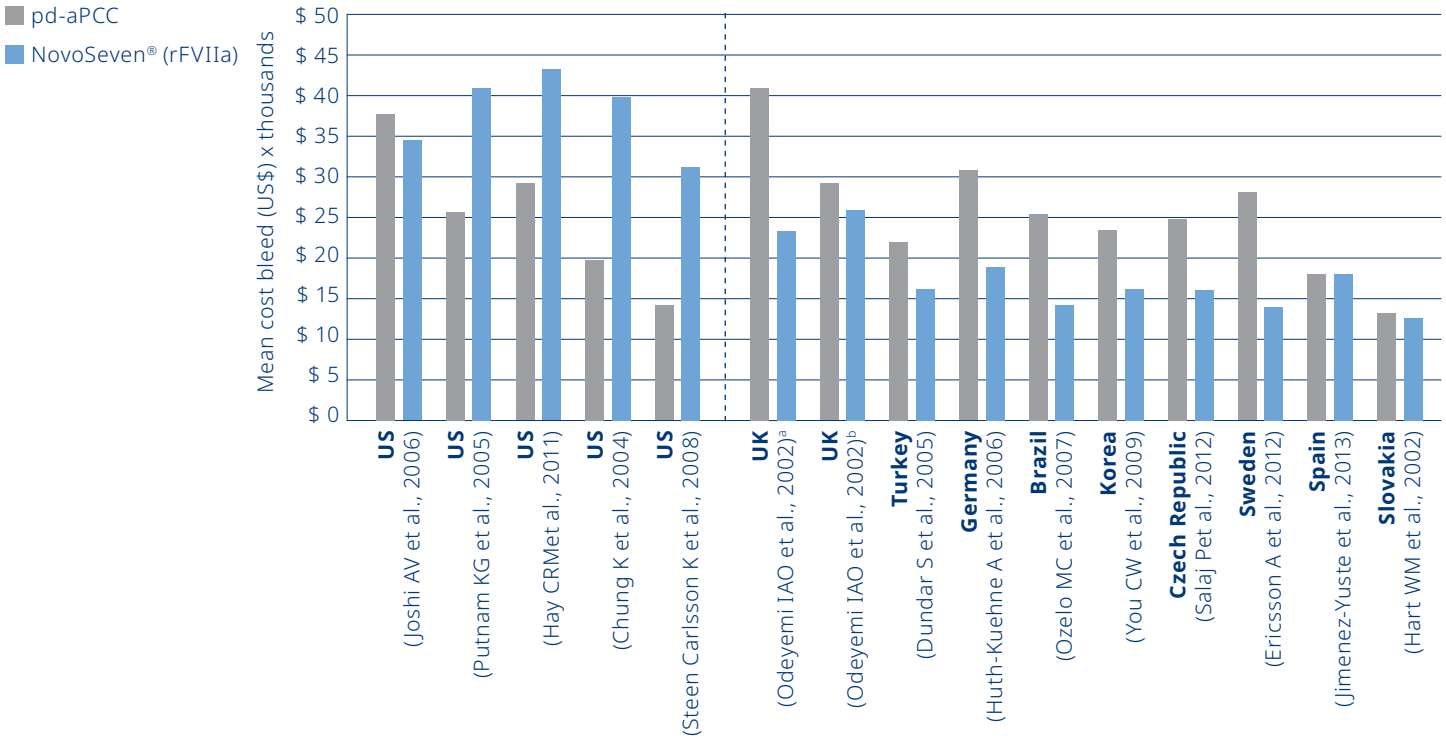
- No cases of thrombotic microangiopathy (TMA) or thromboembolism (TE) were observed with use of NovoSeven® alone in patients receiving emicizumab prophylaxis (n=34). The median cumulative dose of NovoSeven® used was 700.8 µg/kg (range: 89 µg/kg to 15,654 µg/kg) per treatment episode*[5,15,16]

The right choice of BPA for the emergency treatment of bleeds is critical

Can you afford to ignore cost-effectiveness?

NovoSeven® used first-line for emergency bleeds is cost-effective around the world[17–31]

Cost-effectiveness studies comparing pd-aPCC and NovoSeven®



Note: All costs were converted to US dollars and inflated according to the inflation rate per country to reflect 2016 costs.
Source inflation rate: http;//www.oecd.org/; cost-effectiveness results.

- Regardless of the NovoSeven® starting dose used to treat acute bleeding episodes (90 µg/kg or 270 µg/kg), the total dose and drug costs are equivalent[32]
- With no risk of anamnestic response, NovoSeven® can save hospitals up to 20% when used to manage acute bleeds prior to ITI therapy, compared with pd-aPCC[22]
- Stability of NovoSeven® at room temperature may reduce product wastage and associated costs[33]

Prepare yourself for emergencies: stock your hospital pharmacy and treat fast with NovoSeven®

When bleeds happen you need established efficacy...

Unsurpassed effective bleed resolution

96.5% Of responses were rated as effective when treated with NovoSeven® within one hour of bleed onset*†[8]

>4x More patients achieved bleed resolution with a single dose of NovoSeven® 270 µg/kg vs. those treated with pd-aPCC 75 IU/kg (36.4% vs. 8.3%, P=0.032)‡[34]

Established dosing regimen for serious bleeds:

An initial dose of 90 µg/kg of body weight is recommended as early as possible, and could be administered on the way to the hospital[1]

Until clinical improvement is observed

For 1–2 days or until haemostasis

For as long as treatment is indicated

Over 30 years of research and clinical experience[1,13]

* The SMART-7™ study was a prospective, observational, single-arm, multi-centre, multi-national study investigating the safety and effectiveness of roomtemperature-stable NovoSeven® in people with haemophilia A or B with inhibitors in a real-world setting. The primary objective was to monitor reduced therapeutic response and neutralising antibodies to rFVIIa.[8]

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‡ An open-label, randomised, crossover, clinical equivalency study.

...and convenient safety profile

NovoSeven® has a favourable and established safety profile with more than 5.4 million doses administered since 1996[13,32,35–39]

NovoSeven® is the only EMA-approved recombinant bypassing agent containing only rFVIIa and no other coagulation factors, such as FIX or FIXa:[1,40]

- Does not induce an anamnestic response prior to immune tolerance induction (ITI) therapy[41]
- Zero cases of thrombotic microangiopathy (TMA) when used in combination with emicizumab[15]

At pharmacological doses, NovoSeven® directly activates Factor X on the surface of activated platelets only at the site of vascular injury, it is therefore associated with a low incidence of thromboembolic events (TEs):[1,9–12,15,19,42]

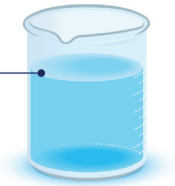
- Regardless of concomitant treatment with antifibrinolytics[1]
- Regardless of concomitant treatment with emicizumab[16]

When treating bleeds time is of the essence[4,6,7]

Low volume, rapid reconstitution and infusion

NovoSeven® has a lower infusion volume, which means rapid reconstitution and rapid infusion compared with pd-aPCC.[2]

84 ml
pd-aPCC
(75 U/kg)[14]



5 ml
NovoSeven®
(90 g/kg)[3]

30 minutes from bleed onset to treatment with NovoSeven®[8]

0 min.
bleed recognised

96.5% efficacy when treated within 1 hour of bleed onset[†‡8]

2–5 min.
to reconstitute (median)[*†2]

+2–5 min.
to infuse[†1]

+10 min.
to peak coagulation[43]

35-40 min.
administration time for reconstituted pd-aPCC[2]

30 min. Median time to first NovoSeven® treatment from bleed onset in SMART-7™[8]

* Patient-reported outcome study (18 adults and 19 caregivers of 21 children) in which frequently bleeding CHwI patients (>4 bleeds in 3 months) or their caregivers were asked to record bleeding episodes, time of start bleed, symptoms, cause, type, location, time of bleed stop, bypassing agent administered for at least 90 days or until 4 bleeding episodes were reported.[2]

† Dose calculation is based on a recommended individual dose of 90 µg/kg body weight for mild-to-moderate joint, muscle and mucocutaneous bleeds, approximately 5 mg. Dose frequency: 2–3 injections administered at three-hour intervals. If further treatment is required, 1 additional dose of 90 µg/kg body weight can be administered.[1]

‡ Post-hoc sub-analysis of SMART-7™ assessed haemostatic response to NovoSeven® in a real world setting where time to first treatment was under 1 hour: a total of 318/618 bleeding episodes treated with rFVIIa monotherapy and with (1) valid efficacy assessment, (2) no missing time for bleed start, (3) no missing time for any dose administration, and (4) valid time to first treatment were included in the analysis. Effective = patient reported that the bleed "stopped"; Partially effective = patient reported that the bleed "slowed"; Ineffective = patient reported that the bleed "worsened / no change".[8]

One solution for many indications in one small box

Practical in-hospital storage and easy portability for out-patients

Pre-reconstitution, NovoSeven® is stable for:[1]

- up to 3 years at <25 °C

Room-temperature stable for portability and easy storage **post-reconstitution**[1]

- 6 hours at 25 °C
- or 24 hours at 5 °C

NovoSeven® has 30 years of research and clinical experience across more indications than any other agent[1,13,14,44,45]

✔ bleed prevention

✔ on-demand treatment of bleeds

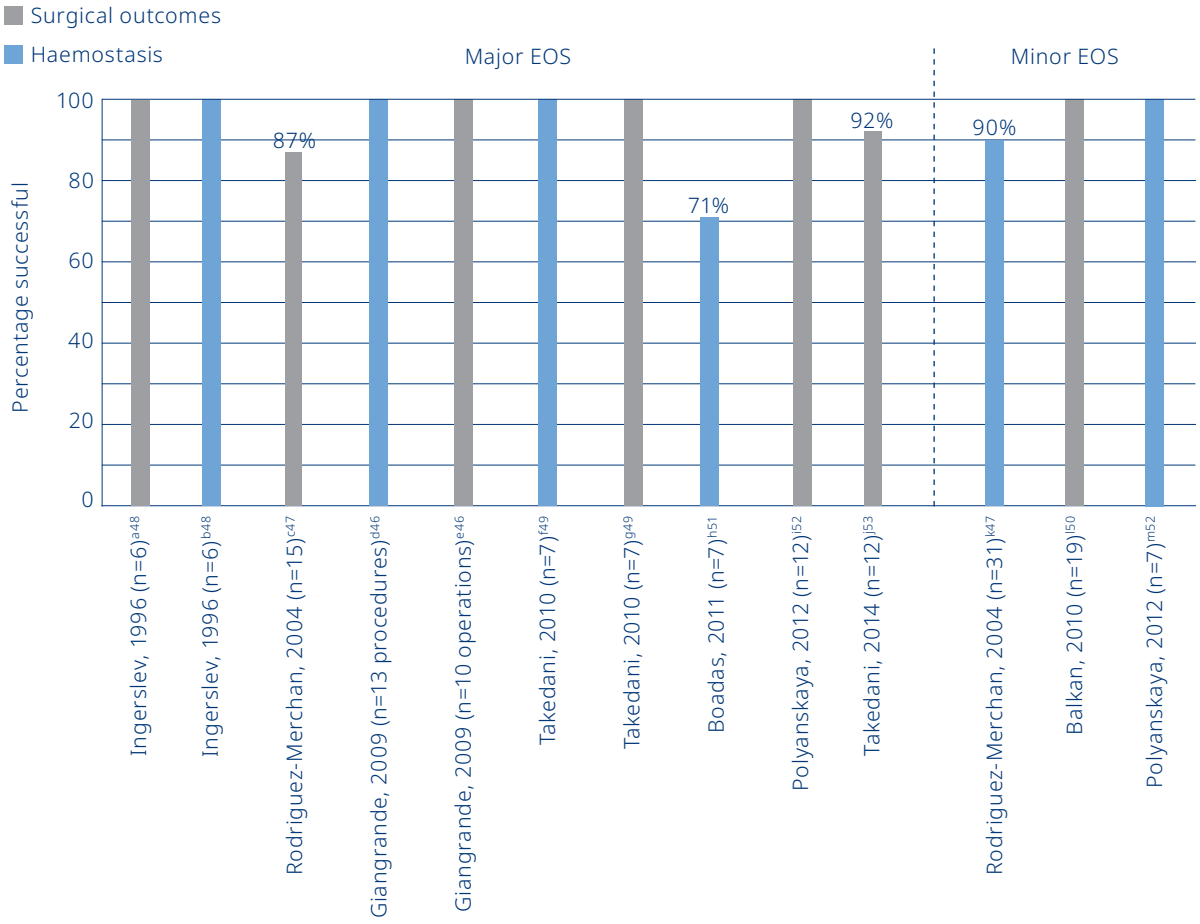
✔ prevention of bleeds during surgeries

	CHAwI		CHBwI		AH	GT	FVIICD
NovoSeven® Recombinant Factor VIIa	>18 years ✔ ✔	<18 years ✔ ✔	>18 years ✔ ✔	<18 years ✔ ✔	✔ ✔	✔ ✔	✔ ✔
FEIBA®14	>18 years ✔ ✔ ✔	<18 years ✔ ✔ ✔					
OBIZUR®					✔		
SEVENFACT®	>18 years ✔		>18 years ✔		✔		

Please confirm local indications for all products, this table is based on EMA approval of NovoSeven®, UK approval of FEIBA®, US approval of Obizur® and SevenFact®. Please adapt for your market when localizing

Rely on NovoSeven® for surgical procedures[1]

Reported efficacy of NovoSeven® during major and minor EOS procedures*[46-53]



This graph illustrates studies identified using the selection and reporting criteria defined below.

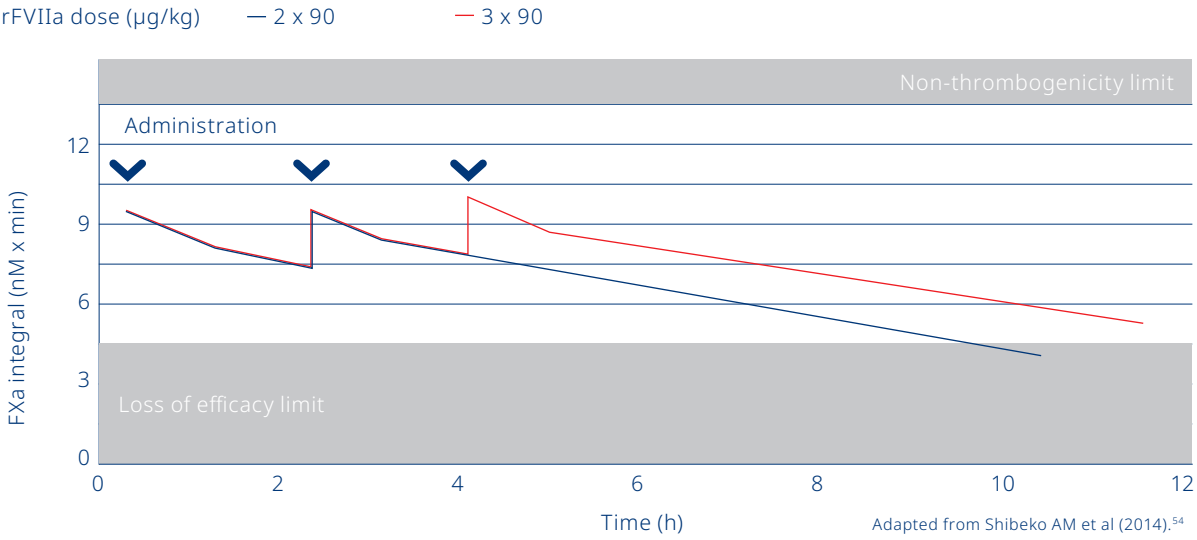
Efficacy shown as percentage successful, defined by the authors as:

a 'Excellent' or 'efficient' global outcome; missing value excluded
b Postoperative haemostasis judged as 'achieved'
c 'Good' or 'fair' outcomes on WFH composite score (pain, bleeding,clinical features, radiological changes)
d 'Excellent' or 'extremely satisfactory' final outcome
e 'Satisfactory' intraoperative haemostasis
f 'Excellent surgical results'
g No unexpected massive bleeding or bleeding complications
h Post-operative haemostasis judged 'effective'
i 'Effective' haemostasis
j 'Complete haemostasis' (composite score of blood loss, postoperative bleeding control and maintained haemostasis)
k 'Good' or 'fair' outcomes on WFH composite score (pain, bleeding, clinical features, radiological changes)
l 'Good' response to treatment (no need for transfusion)
m 'Effective' haemostasis

*** Study selection and reporting criteria**

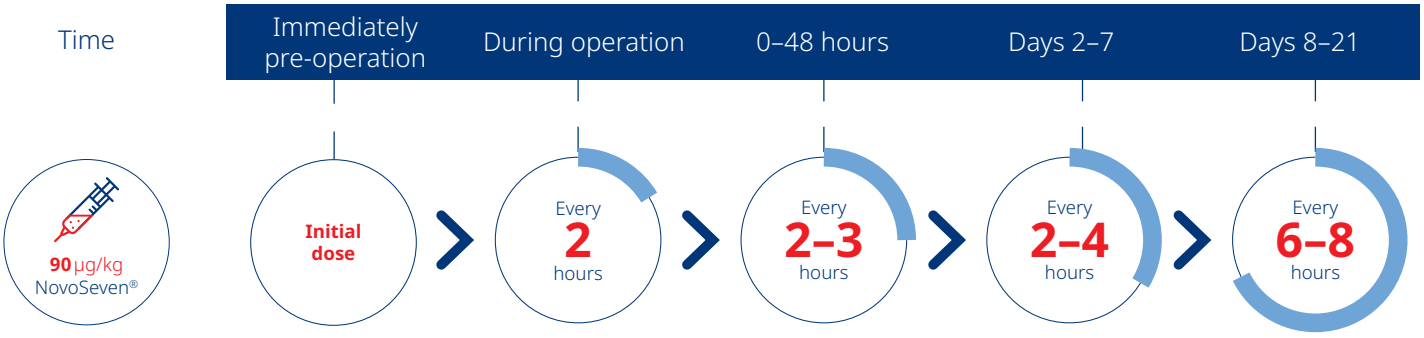
- Reviewed studies reporting ≥ 4 major or minor EOS procedures
- Used the author's definition of minor and major EOS
- Included procedures where outcome of individual procedures could be identified
- rFVIIa used as bolus dose and not in combination with another bypassing agent
- Only EOS procedures reported (non-EOS and pseudotumours excluded)

Possibility to re-dose every 2–3 hours during the surgery and for the (48-hour) immediate postoperative period*†[54]



Adapted from Shibeko AM et al (2014).[54]

Dosing for bleed control in surgery[1]



More than 400 successful surgical procedures performed with NovoSeven® reported in a range of studies[46-53,55-69]

* Post-operative bleeding can be a result of inappropriate treatment regimens, which can be resolved by increasing or adding additional doses of bypassing agent.

† It is important to consistently administer NovoSeven® as prescribed as missed or delayed doses can leave patients vulnerable to rebleeds.

1 Start with NovoSeven® when you need rapid bleed control at the hospital[1]

Rapid bleed control with consistently high efficacy[70]

- The only bypassing agent with 89%–93% efficacy demonstrated across 4 indications[70-74]

Favourable safety profile across all approved indications[12,36,75]

- Established in 30 years of research and experience[12,36,75]
- Low rate of thrombotic events, due to targeted mechanism of action[36]

Rapid reconstitution and administration[1,2]

- Rapid reconstitution: 5 minutes (median)[2]
- 2–5 minutes to inject[1]

* The chemical and physical in-use stability of NovoSeven® has been demonstrated for 24 hours at 25 °C in a 50 ml syringe (polypropylene). When administered by pump, a CE-marked infusion pump must be used. All steps for reconstitution and administration should be completed under controlled and validated aseptic conditions by adequately trained personnel. 50 ml polypropylene syringe for automated bolus injection is not provided in the NovoSeven® package. For further details, please refer to 'Procedure for pooling of vials for hospital use only' in the Summary of Product Characteristics.[1]

† Any CE-marked pump capable of delivering regular, automated injections can be used via a [50 ml] polypropylene syringe, including hardware already available in hospitals.[1,77] The pump should be replenished once per 24 h,[1,76] or in accordance with pump manufacturer and hospital guidelines.

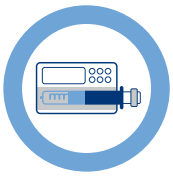
** Please consult the relevant SPC for specific dosing in individual indications. Schematics are not drawn to any scale.

‡ Guidelines for replenishing and programming pumps may differ depending on the model used. Please consult your individual hospital's protocol.

Stay in control with NovoSeven® through to discharge[1]

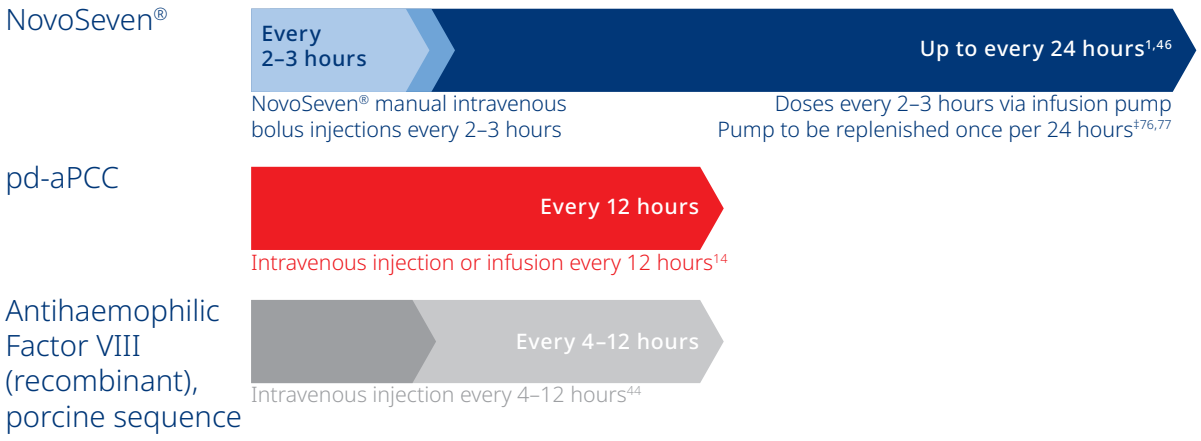
NovoSeven® is physically and chemically stable post-reconstitution when stored in a 50 ml syringe (polypropylene) for automated bolus injection for 24 hours at 25 °C*†[1,77]

- Specific activity within acceptance criteria[77]
- Very limited product degradation[77]
- No changes in transparency, colour or presence of sedimentation[77]
- No microbiological growth detected[77]



NovoSeven® can now be delivered at the hospital by automated bolus infusion pump for the right dose at the right time†[77]

Administration recommendations according to SPCs (hospital use)[**1,14,44]**



NovoSeven® administration by automated bolus infusion pump at the hospital can offer a number of benefits*†[76]

Effective

Ensure consistent efficacy with the right dose at the right time[54,76,78,79]

- Delayed or missed doses can leave patients vulnerable to rebleeds[54,76,78,79]
- Automated administration of the right dose at the right time can give confidence to the MDT that haemostasis will be maintained throughout the procedure[54,76,78,79]

Effortless

Minimise disruption to patients during recovery[76]

- An automated bolus infusion pump can administer doses throughout the night and avoid waking the patient, supporting rest and recuperation[76]

MDT – Multidisciplinary team

Efficient

Reduce burden of reconstitution and administration for nurses[76]

- Reconstitution may only be required once per 24 hour period,**[76] allowing for a considerable reduction in nursing time with automated administration[76]
- Nurse's anxiety about making medication errors can also be decreased[79]

Economic

Precise dosing could reduce overconsumption[76]

- In a study involving two patients receiving NovoSeven® via an automated bolus infusion pump post-operatively, savings were estimated at up to 50 mg[76§]

* The chemical and physical in-use stability of NovoSeven® has been demonstrated for 24 hours at 25 °C in a 50 ml syringe (polypropylene). When administered by pump, a CE-marked infusion pump must be used. All steps for reconstitution and administration should be completed under controlled and validated aseptic conditions by adequately trained personnel.[†]

[†] Compared with manual intravenous bolus injections.

** Guidelines for replenishing and programming pumps may differ depending on the model used. Please consult your individual hospital's protocol.

[§] The rounding up of doses when administering individual intravenous bolus injections can result in overconsumption. 50.4 mg overall savings observed across two patients for doses delivered with the automated bolus infusion pump compared with individual manual bolus doses.[76]

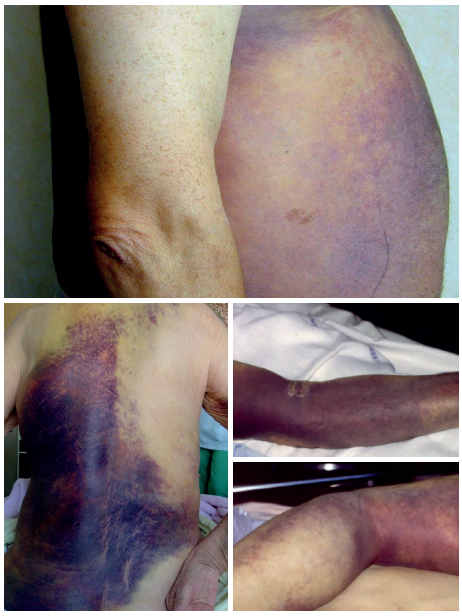
Consult: Urgent laboratory diagnosis is required when unexplained bleeding or bruising occurs[80-82]

AH occurs when the immune system develops inhibitors for the body's clotting factors, most commonly FVIII[80]

80% of patients present with widespread subcutaneous bleeds[81]

- Other soft tissue and mucosal bleeding is also common[81]

Extensive subcutaneous bleeding requires urgent laboratory investigation[80-82]



Effective haemostatic treatment can save lives[71,83]

	Green, 1981[84]	EACH2, 2012[71]	SACHA, 2013[85]	Kruse Jarres, 2015[86]	HTRS, 2016[87]	ACQUI-7, 2016[88]	Jayakar, 2018[89]
Patients, n	215	219	82	28	68	27	40
Mortality due to bleeding	22%	3.3%	3.5%	10.7%	0%	3.7%	0%

Confirm:
Three tests confirm a diagnosis of AH:[80,81,90-92]

		Abnormal result	Normal range[91-93]
1	aPTT Test ↓ aPTT mixing test (2 hours incubation at 37°C) ↓ Consider pharmacological anticoagulant Consider lupus anticoagulant	Isolated prolonged aPTT >40 seconds	25–40 seconds*
2	↓ FVIII:C activity	Low FVIII levels	50–200%
3	↓ Bethesda assay	Presence of FVIII inhibitors	<0.7 BU

Adapted from: Tiede A et al. Semin Thromb Hemost 2014.[94]

Always establish the cause of a prolonged aPTT (e.g. >40 seconds**), irrespective of the clinical presentation[71,73]

* Normal range varies depending on the testing laboratory
** Refer to the standard range provided by testing laboratory

Control: Your primary treatment objective in AH is to stop the bleed[1]

- More than 30 years of clinical experience[1,13]
- More than 1,000 bleeds in 671 patients treated[95]
- Consistently high efficacy, proven in 6 major registries and studies[71,88,96-99]

Compassionate use programme in AH[97]
Multicentre study
1990–1995

EACH2[71]
European Acquired Haemophilia Registry
2003–2008

Japanese PASS[96]
Single-centre post-marketing surveillance study
2000–2010

Acqui-7[88]
Single-centre post-marketing surveillance study
2000–2010

Compassionate use HRTS/HTRS, literature[98]
Retrospective review of a longitudinal database
1988–2005

AHS[99]
Simple IRB-exempt case report surveillance system to supplement HTRS registry
2008–2011

KEY

Complete or partial response

Bleeds resolved

A median of 36 hours to bleed resolution with NovoSeven®*[71]

EACH2 dosing of first-line haemostatic therapy for all first bleeding episodes (median [interquartile range])[71]

	n	Baseline FVIII level, IU/dL	Baseline inhibitor titer, BU/mL	Initial dose, µg/kg or U/kg	Initial dosing interval, hours	Total doses per patient, n	Total doses per patient
NovoSeven® Recombinant Factor VIIa	**174**	**2.0** (0.0–32.0)	**15.5** (1.0–2.765)	**90 µg/kg** (84.71–102.86)	**3** (2–6)	**12** (3–35)	**84 mg** (24–216 mg)
pd-aPCC	**63**	**1.0** (0.0–40.0)	**18.0** (0.1–1.700)	**66.67 µg/kg** (52.63–82.19)	**12** (12–12)	**8** (3–15)	**30 000 U** (12 000–56 000 U)

A median of 96 hours to bleed resolution with pd-aPCC**

* Median time to bleed resolution based on initial dosing interval (3 hours) x total doses per patient (12 doses)
** Median time to bleed resolution based on initial dosing interval (12 hours) x total doses per patient (8 doses)

NovoSeven® is easy to use, convenient and portable, enabling reconstitution with fewer steps*[1,100]

NovoSeven® dosing schedule[1]

Full administration in 2–5 minutes[1]
Peak coagulation ability in 10 minutes[101]

Until haemostasis is achieved

Successively increase dose interval
for as long as treatment is judged to be indicated

NovoSeven® dose frequency can be adjusted based on severity of bleeding condition and clinical response

- No need for real-time monitoring[1]
- Allows use of standard laboratory services
- NovoSeven® administration by automated bolus infusion pump at the hospital can offer a number of benefits*†[16]

* Compared with NovoSeven® vial-to-vial reconstitution.
† In the hospital setting.
‡ Based on the initial dose for a 56-kg patient with acute bleeding.

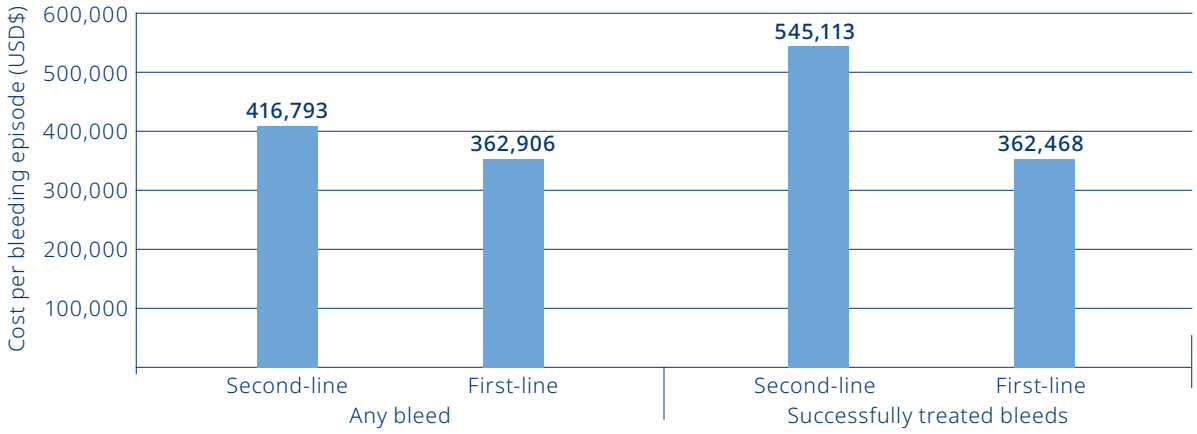
Favourable safety profile established over 30 years[1,13,71,75,83,95,102]

- Works locally at the site of vascular injury[1]
- Low rate of thrombotic events in a high-risk population (2.9%)[71,102,103]
- Experience with concomitant administration of antifibrinolytics and rFVIIa treatment is limited[1]
- Does not induce anamnesis[104]
- No inhibitory antibodies to NovoSeven® were reported in post-marketing experience[81]
- No risk of transferring blood-borne human pathogens[13,104]

NovoSeven® – Cost-effective in first-line treatment of severe bleeds[105]

Because of NovoSeven®'s high efficacy and a median time to bleed resolution of 36 hours, the biggest overall drivers of costs are the treatment failures of other therapies when they are used first line instead of NovoSeven® [105,85]

Costs per bleeding episode in first- and second-line treatment with NovoSeven® in patients with acquired haemophilia*[105]



Adapted from Odeyemi and Dano 2008.

- First-line treatment was cost-effective compared with second-line treatment based on an improved efficacy rate (100% vs. 75%) and a reduction of the costs per bleed[105]

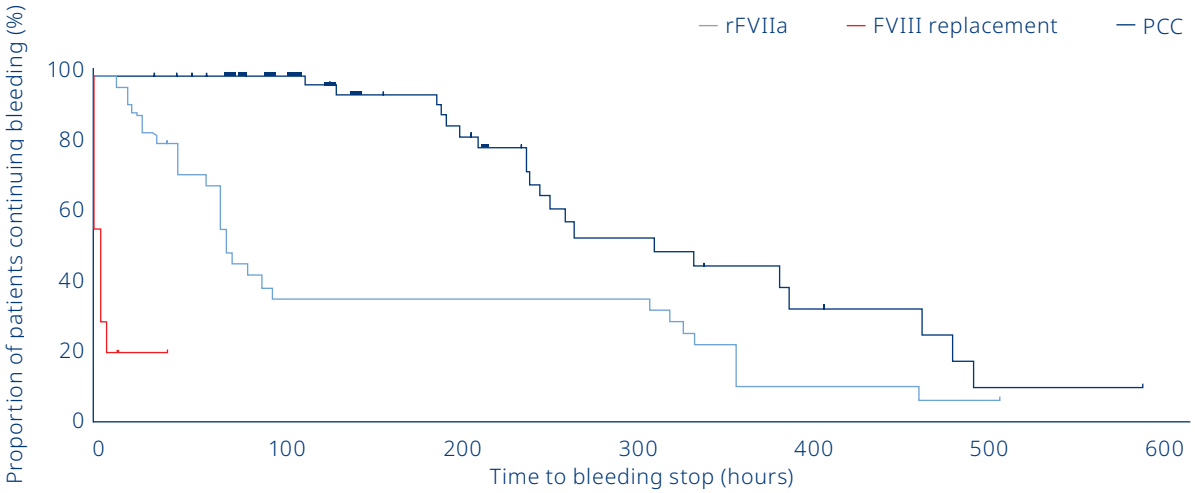
* Cost effectiveness study comparing use of NovoSeven® first line vs. second line in patients with acquired haemophilia in the US. Costs were calculated based on 2007 USD unit costs.

USD – US dollar

Unnecessarily long hospitalisations may incur extra costs[82]

The China Acquired Hemophilia Registry (CARE) was a nationwide multicentre registry in which treatment for acquired haemophilia was assessed[82]

A shorter time to bleed resolution may be cost saving



Data regarding the time to cessation of bleeding was available for 9 patients treated with NovoSeven®[82]

- The median time to cessation of bleeding was 5 hours (interquartile range, 2.5–6.75 hours) for patients treated with NovoSeven®
- In 2 patients not responding to PCC as initial therapy, bleeding was resolved after receiving NovoSeven®
- Of the 40 patients for whom initial FVIII replacement therapy failed, 4 patients received NovoSeven® and bleeding was resolved in all of them

  23 patients received PCC as salvage therapy, of whom 5 did not respond. Of these 5 patients, bleeding was controlled in 3 with NovoSeven®

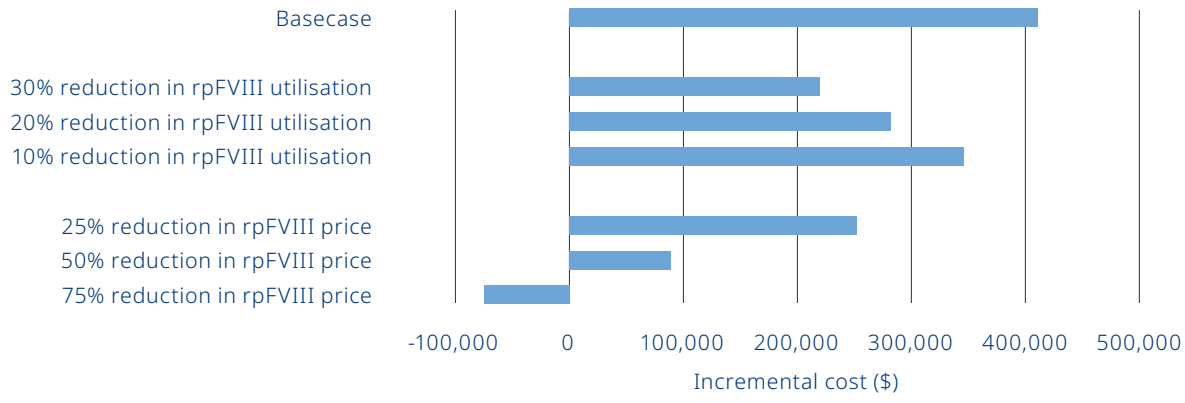
PCC – prothrombin complex concentrate

NovoSeven® – Cost-effectiveness vs. other options[83,106]

A simulation model (based on US average sales prices, $) found that, in a hypothetical cohort of 1,000 patients with AH:*[83,106]

	NovoSeven®	rpFVIII
Bleeds controlled in patients initiating with this product	90% (95% CI: 83–96)	90% (95% CI: 79–98)
Estimated discounted lifetime costs	$264,000	$672,000
QALYs	6.77 (95% CI: 6.07–7.48)	6.56 (95% CI: 5.38–7.63)

Incremental cost of rpFVIII vs. NovoSeven®†



Adapted from Oladapo 2017.

- Inhibitors in acquired haemophilia can cross react with rpFVIII in up to 44% of patients[107]
- This may result in increased clearance of the product, reduced efficacy and a need for increased product consumption[107]

* Proportion of patients from the simulated cohort treated with second-line therapy: 39%.
† Results should be interpreted with caution, as sources from which input data were drawn may not be comparable due to differences in methodology, and possible differences in acquired haemophilia A severity and related comorbidities.

AH – acquired haemophilia; CI – confidence interval; QALY – quality-adjusted life year; rpFVIII – recombinant porcine sequence factor VIII

Consult. Confirm. Control with NovoSeven®

Rapid bleed control with consistently high efficacy[71,96,99,101]

Established safety profile[1,13,71,75,95,102]

Simple, rapid reconstitution and administration, and convenient storage*[1]

NovoSeven® has demonstrated cost-effectiveness

- In the first-line treatment of severe bleeding episodes in patients with acquired haemophilia[105]
- Vs. other options in acquired haemophilia A[106]

Glanzmann's thrombasthenia treatment is moving ahead[108]

The European Medicines Agency (EMA) has extended the label* of NovoSeven® to:†[108]

- patients with Glanzmann's thrombasthenia (GT) with past or present refractoriness to platelets
- or where platelets are not readily available

* In the treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures.

† Previous label stated: NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in patients with Glanzmann's thrombasthenia.

(GT) with antibodies to GP IIb – IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.

NovoSeven®: Rapid bleed control with consistently high efficacy in GT[72,109]

Rapid bleed control with consistently high efficacy for on demand treatment of bleeds and surgery in patients with GT[72,109]

Favourable safety profile across 30 years of research and experience across all approved indications[§13,36]

Convenient fast, low volume administration[¶108]

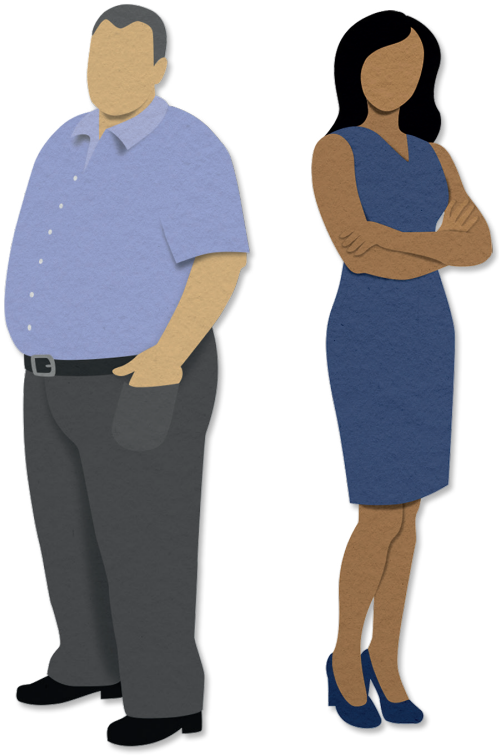
* In the treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures.
† Previous label stated: NovoSeven® is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in patients with Glanzmann's thrombasthenia (GT) with antibodies to GP IIb - IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.
‡ In patients with GT with or without refractoriness.
§ Development of NovoSeven® began in June 1985.
¶ 6 ml in 70 kg 2–5 min bolus infusion.

GT is rare and may be underdiagnosed[110,111]

GT affects approximately 1 in 1 million people[112,113]

- GT is a rare platelet function disorder caused by an abnormality in the genes coding for glycoproteins IIb/IIIa[112]
- Glycoproteins IIb/IIIa can be found on the surface of platelet membranes[113]
- The dysfunction or absence of these glycoproteins means that the platelets are unable to effectively aggregate, resulting in bleeding[36]

Bleeding at different sites is often seen in GT[114]



GT= Glanzmann's thrombasthenia. GPIIb-IIIa=glycoprotein IIb-IIIa.

GT may be difficult to diagnose[110]

The diagnosis includes:[113]

- Normal platelet count (typically on the lower end of normal)
- Prolonged bleeding time
- Prolonged platelet function assay time
- Platelets fail to aggregate under the conditions utilised in the light transmission aggregometry test

Frequency of bleeding problems in patients with GT[112]

98% Menorrhagia

86% Easy bruising, purpura

73% Epistaxis

55% Gingival bleeding

12% Gastrointestinal haemorrhage

6% Haematuria

3% Haemarthrosis

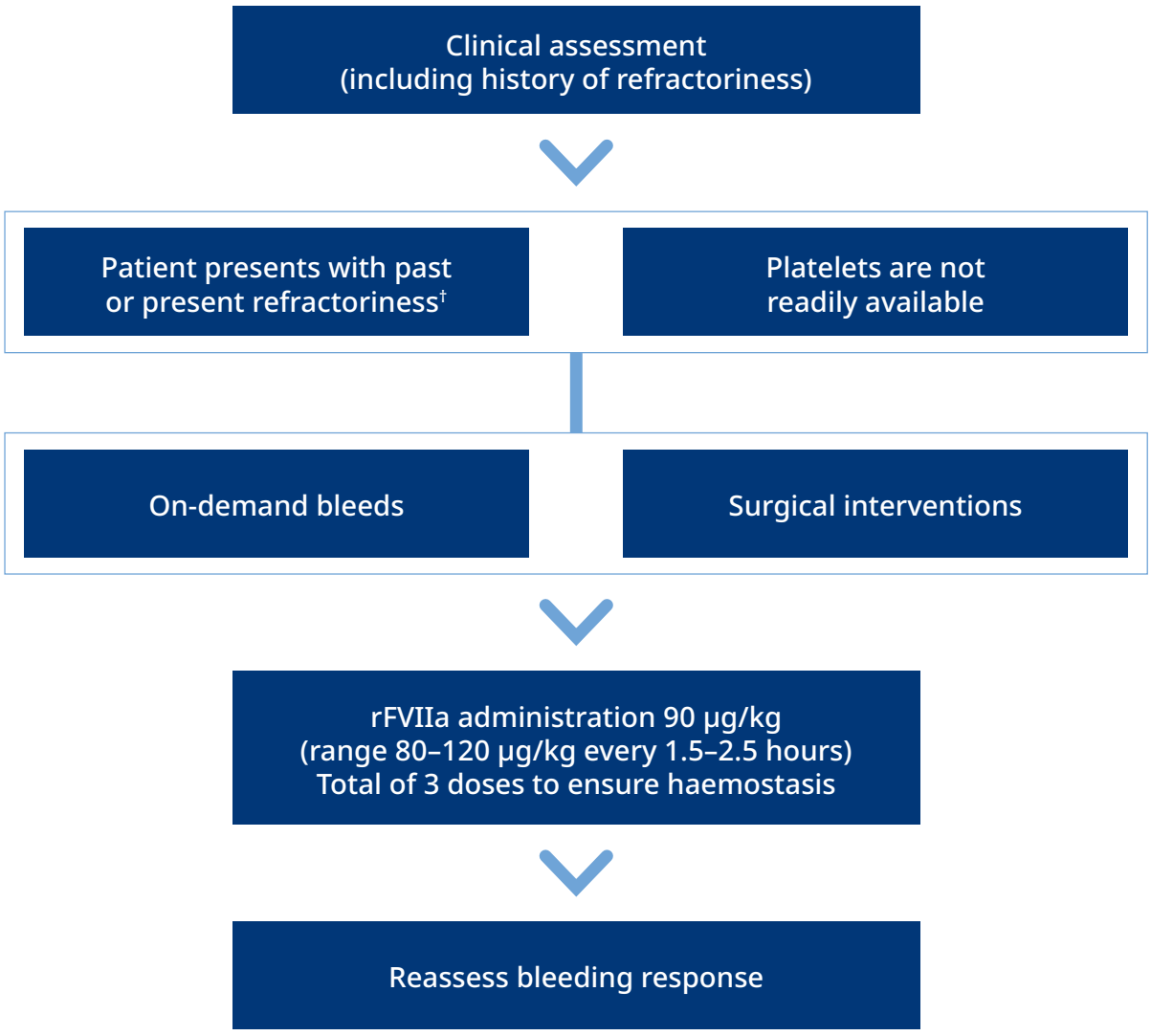
2% Intracranial haemorrhage

1% Visceral haematoma

Percentages represent the proportion of patients (total=43) with GT experiencing each type of bleeding episode in a retrospective survey.[110]

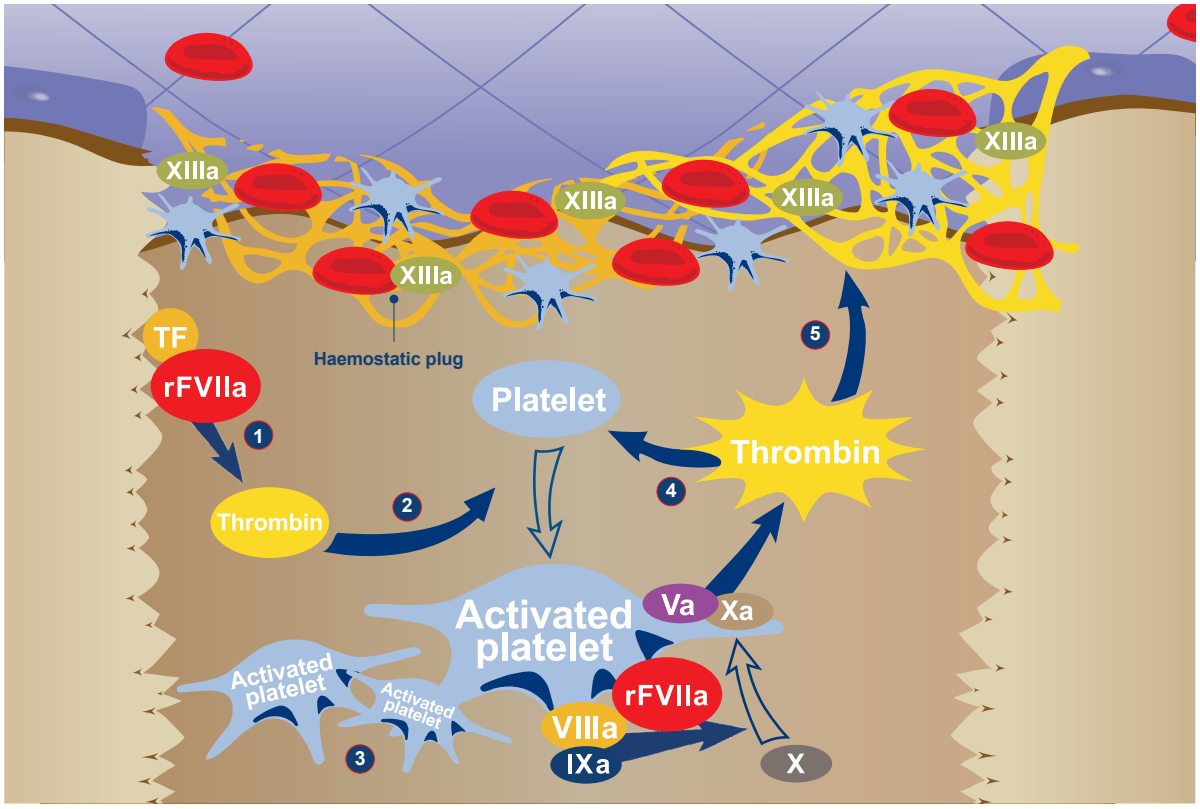
GT= Glanzmann's thrombasthenia.

NovoSeven® supports your GT patients with past or present refractoriness or when platelets are not readily available[108]*



GT=Glanzmann's thrombasthenia; rIIVa=recombinant factor IIVa.
* Hypothetical treatment pathway – based on the EMA label update.
† For those patients who are not refractory, platelets are the first line treatment for Glanzmann's thrombasthenia.

NovoSeven® provides a fast-acting, uniquely targeted mode of action in GT[108,115-118]



1 NovoSeven® enhances local TF-dependent thrombin generation[115,116,118]

2 High levels of NovoSeven® increase the likelihood of platelet activation...[115,118]

3 ...and may also enhance GPIIb-IIIa-independent platelet aggregation[117]

4 NovoSeven® can bind to platelets via TF-receptor GPIba or directly to the partially activated platelet surface and increase the likelihood of thrombin generation and platelet activation[118]

5 NovoSeven® increases local fibrin deposition at the site of injury, contributing to effective clot formation and helping to stop the bleed[115]

GPIbα=glycoprotein Ibα; GPIIb-IIIa=glycoprotein IIb-IIIa; GT=Glanzmann's thrombasthenia; HLA=human leukocyte antigen; TF=tissue factor.

NovoSeven® provides rapid bleed control with consistently high efficacy in GT[72,109]

Results from the GT Registry demonstrated consistent high efficacy of NovoSeven® in the treatment of bleeding episodes and prevention of bleeds in surgery in patients with GT[72,109*]

Treatment of bleeding episodes[72]

Effective in GT with refractoriness[72†]

Effective in GT without refractoriness or antibodies[72†]

Prevention of bleeds in surgery[109]

Effective in GT without refractoriness or antibodies[109‡]

Effective in GT with refractoriness[109‡]

GT=Glanzmann's thrombasthenia.

* The GTR is an observational registry (F7HAEM-3521) covered 133 subjects with Glanzmann's thrombasthenia treated with NovoSeven®. The median dose per infusion for treatment of 333 bleeding episodes was 90 µg/kg (range 28 to 450 µg/kg). NovoSeven® was used in 157 surgical procedures, at a median dose of 92 µg/kg (up to 270 µg/kg). Treatment with NovoSeven®, alone or in combination with antifibrinolytics and/or platelets, was defined as effective when bleeding was stopped for at least 6 hours. All surgeries were minor and all bleeds were moderate in severity.

† Used alone not in combination with other treatments.

‡ Used alone not in combination with other treatments. All surgeries were minor.

NovoSeven® provides convenience for home- and hospital-based treatment[32,108,119]

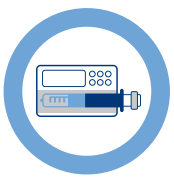
It is recommended to administer at least 3 doses of NovoSeven® to secure effective haemostasis.[111]

Convenient for home-based treatment

- Fast and convenient reconstitution with pre-filled syringe and broad range of vial sizes[100,111]
- Rapid administration in 2–5 minutes[111]
- Portable and easy to store with 3 years stability at <25 °C[111]

Convenient for hospital-based treatment

- NovoSeven® is physically and chemically stable post-reconstitution when stored in a 50 ml syringe (polypropylene) for automated bolus injection for up to 24 hours at 25 °C[77,111*†]
- Bolus doses of NovoSeven® can now be delivered at the hospital by automated bolus infusion pump for the right dose at the right time[77†]



RT =room temperature.

* In-use stability of NovoSeven® has been demonstrated for 24 hours at 25 °C in a 50 ml syringe (polypropylene). 50 ml polypropylene syringe not provided in the NovoSeven® package. For further details, please refer to the Summary of Product Characteristics.[108]

† Any CE-marked pump capable of regular, automated injections can be used via a 50 ml polypropylene syringe, including hardware already available in hospitals.[108,119] The pump should be replenished once per 24 h,[100,108] or in accordance with appropriate guidelines.

NovoSeven®: Rapid bleed control with consistently high efficacy

In congenital factor VII deficiency (cFVIID)[73,120]

Rapid bleed control with consistently high efficacy[73,121]

Favourable safety profile using recombinant technology[1,36,104]

Fast, low volume administration[1]

NovoSeven® provides flexible dosing for bleed control and prevention of bleeding in surgery or invasive procedures[1+]

Until haemostasis

+ Dose and frequency of injections should be adapted to each individual

New! NovoSeven® for severe postpartum haemorrhage (PPH) when uterotonics are not sufficient to stop the bleed.[1]

High unmet need: severe PPH is highly prevalent* and the #1 cause of maternal mortality[122]

One woman dies from postpartum hemorrhage every 7 mins[123]

77% of post-partum ICU admissions attributed to PPH[124]

Every year in Europe:
- 70'000 cases of sPPH
- 4'000 hysterectomy
- 38 deaths

Worldwide, PPH accounts for[125]:
- 8% of maternal deaths in developed regions of the world
- 20% of maternal deaths in developing regions

Complications following severe PPH are often critical and can include[123]
- Organ failure
- Thrombo-embolic events (TE)
- Hemorrhagic shock
- Hysterectomy
- Loss of fertility

* 1-3% of live births in Europe[126]

High unmet need: Diagnosis and treatment gaps

While there are known risk factors, the impossibility of accurately identifying the women at risk of PPH justifies the application of prevention strategies to all.[127]

- Healthcare professionals may underestimate blood loss by 30-50%[128]
- PPH is assessed subjectively 95% of the time[129]
- Where sPPH is objectively assessed, the prevalence of births with sPPH (>1000 mL) is almost double what is seen when subjectively assessed 3.04% vs 1.68% of live births[129]
- No single definition for severe PPH[130-133]

Delayed action may lead to invasive procedures (including hysterectomy) associated with complications.[134-137]

Most efficacious interventions are used last to avoid long-term complications.[134-137]

Birth | PPH | Severity[1] of PPH increases if bleeding not controlled

Obstetric Ward | Surgery / OR

High unmet need: hysterectomy, blood transfusion and haemostatic agents

Hysterectomy

Hysterectomy leads to a maternal morbidity varying between 26 and 44% and up to 13% maternal mortality[134,135,137]

It is associated with injuries to surrounding organs that can lead to vaginal problems, ovarian failure and early menopause[134,135]

Complete loss of fertility with psychological and social implications[134,135,137]

Blood transfusion

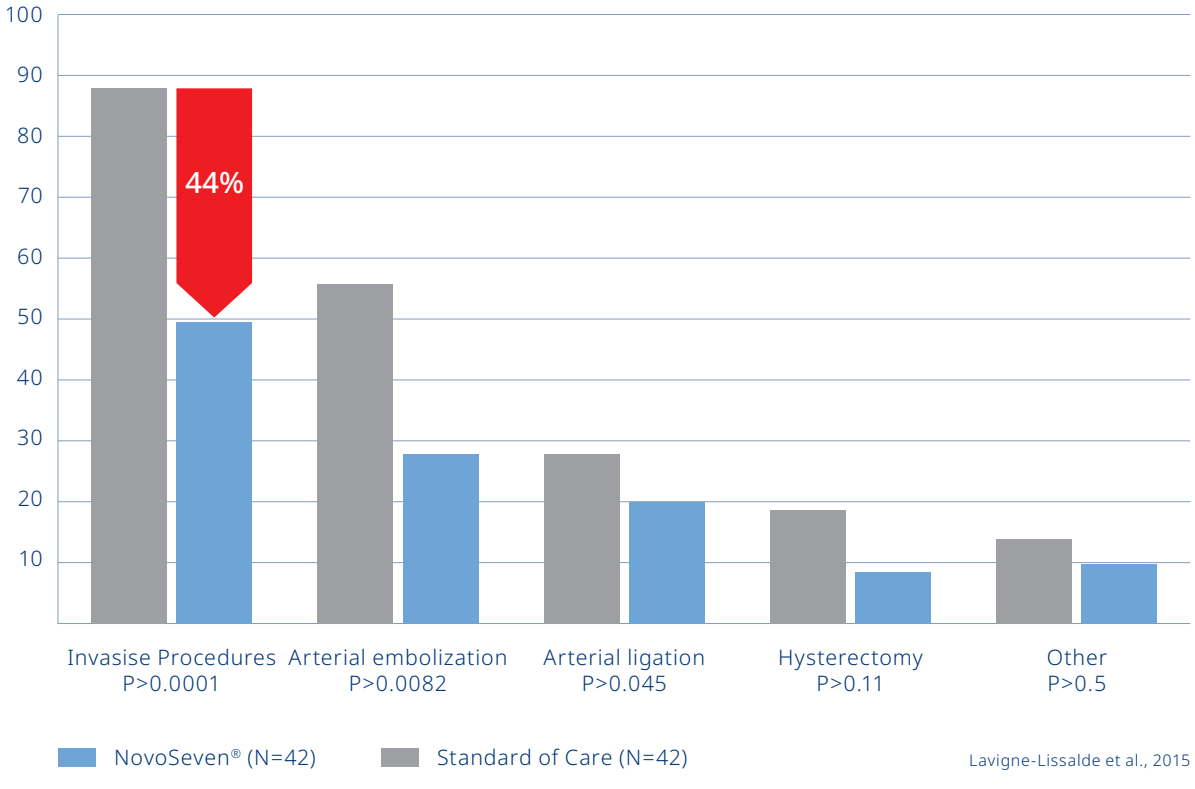
Blood transfusions and blood product administration carry substantial medical risks e.g. post-operative infection, transfusion immune reactions, TE, transfusion-transmitted infections[138-140]

Availability is limited, low and middle-income countries especially are often unable to meet the demand for blood and blood products[139-141]

NovoSeven®: your team's fast, non-invasive option to control severe PPH*

Lavigne-Lissalde et al. found a 44% reduction (P<0.0001) in relative risk for any invasive procedure[142]**
(sutures, ligation, embolization, hysterectomy, balloon)

No difference seen in efficacy by mode of birth[142]
(C-section vs. vaginal delivery)

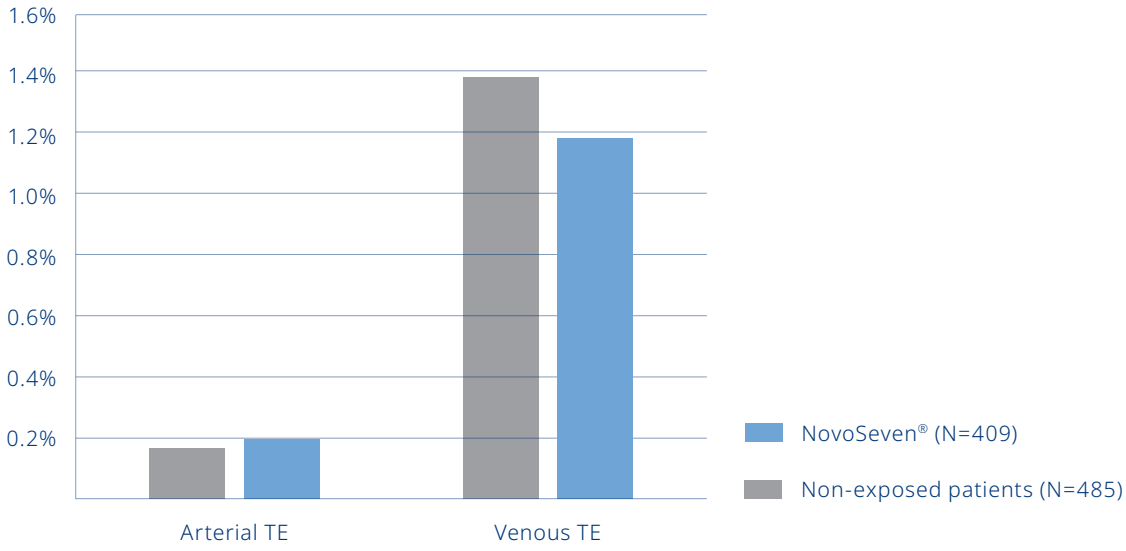


Lavigne-Lissalde et al., 2015

* After failure of uterotonics
** Invasive procedures include: uterine arterial ligation, embolisation, uterine compression sutures, balloon and hysterectomy

NovoSeven®: no observed elevation in TE risk vs. non-exposed†

- Real world rate of TE (1.1%*) observed in 4 observational studies (OS) (N=358)[1]
- Short terminal half-life (2 hours)[1]
- Acts on platelets at the site of injury[1]
- No contraindication to co-administer with tranexamic acid and/or fibrinogen[1,142**]



† In 409 NovoSeven® exposed and 485 non-exposed women: 0.2% for ATEs in both groups, and 1.2% versus 1.4% for VTEs in exposed and non-exposed women respectively)

* In 4 non-interventional studies, venous thromboembolic events were reported in 3 of 358 (0.8%) patients treated with NovoSeven (median dose range 63-105 µg/kg) and arterial thromboembolic events were reported in 1 (0.3%) patient treated with NovoSeven. Rate of all TE combined was 4 of 358 (1.1%).[3]

** Fibrinogen and tranexamic acid were part of standard of care in the RCT and about 40% of the patients with available information received fibrinogen and/or tranexamic acid in the NovoSeven® exposed and control arm.

NovoSeven®: Treat fast. Avoid potential complications

44.7%* reduction (P<0.0001) in invasive procedures[143]
(uterine compression sutures, arterial ligation, embolization, hysterectomy)

Meta-analysis of safety data from 1 RCT and 4 observational studies indicates no increased risk of TEs[143]

Formulated to treat fast (<5 min) and achieves peak effect in 10 minutes[143]

* Observational studies did not provide additional support for this outcome using PS algorithm (possibly explained by differences in patient populations, later administration of rFVIIa and potential imbalance in PS matched groups)

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Abbreviated Summary of Product Characteristics

Consult Summary of Product Characteristics before prescribing.
Presentation: NovoSeven® 1 mg (50 KIU) powder and solvent (pre-filled syringe) for solution for injection. NovoSeven® 2 mg (100 KIU) powder and solvent (pre-filled syringe) for solution for injection. NovoSeven® 5 mg (250 KIU) powder and solvent (pre-filled syringe) for solution for injection. NovoSeven® 8 mg (400 KIU) powder and solvent (pre-filled syringe) for solution for injection.
Composition: eptacog alfa (activated) is recombinant coagulation factor VIIa (rFVIIa) produced in baby hamster kidney cells (BHK Cells) by recombinant DNA technology, 1 mg/vial, 2 mg/vial, 5 mg/vial, 8 mg/vial (corresponds to 50 KIU/vial, 100 KIU/vial, 250 KIU/vial, 400 KIU/vial). 1 mg/ml eptacog alfa (activated) after reconstitution.
List of excipients: *Powder:* Sodium chloride, Calcium chloride dihydrate, Glycylglycine, Polysorbate 80, Mannitol, Sucrose, Methionine, Hydrochloric acid, Sodium hydroxide Solvent: Histidine, Hydrochloric acid, Sodium hydroxide, Water for injections.
The medicinal product contains less than 1 mmol sodium (23 mg) per injection, indicating that it is essentially 'sodium free'.
Indications: treatment of bleeding episodes and prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:
- patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX >5 BU;
- patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration;
- patients with acquired haemophilia;
- patients with congenital FVII deficiency;
- patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available

Severe postpartum haemorrhage**:** NovoSeven is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis.
Posology: *Haemophilia A or B with inhibitors or expected to have a high anamnestic response:*
Mild to moderate bleeding episodes (including home therapy): Early intervention has been shown to be efficacious in the treatment of mild to moderate joint, muscle and mucocutaneous bleeds. Two dosing regimens can be recommended: 1) Two to three injections of 90 µg per kg body weight administered at three-hour intervals. If further treatment is required, one additional dose of 90 µg per kg body weight can be administered 2) One single injection of 270 µg per kg body weight. The duration of the home therapy should not exceed 24 hours. There is no clinical experience with administration of a single dose of 270 µg
Serious bleeding episodes: An initial dose of 90 µg per
could be administered on the way to the hospital where
lowing dose varies according to the type and severity o
should initially be every second hour until clinical improve
is indicated, the dose interval can then be increased to 3
interval can be increased successively to every 4, 6, 8 o
judged as being indicated. A major bleeding episode ma
extended beyond this if clinically warranted. Invasive procedure/surgery: An initial dose of 90 µg per kg body weight should be given immediately before the intervention. The dose should be repeated after 2 hours and then at 2–3 hour intervals for the first 24–48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2–4 hour intervals for 6–7 days. The dose interval may then be increased to 6–8 hours for another 2 weeks of treatment. Patients undergoing major surgery may be treated for up to 2–3 weeks until healing has occurred. *Acquired Haemophilia:* NovoSeven® should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight. Following the initial dose of NovoSeven® further injections may be given if required. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage, the invasive procedures or the surgery being performed. The initial dose interval should be 2–3 hours. Once haemostasis has been achieved, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged to be indicated. *Factor VII deficiency:* The recommended dose range is 15–30 µg per kg body weight every 4–6 hours until haemostasis is achieved. Dose and frequency of injections should be adapted to each individual. Limited clinical experience in long term prophylaxis in paediatric population has been gathered in the paediatric population below 12 years of age, with a severe clinical phenotype. Dose and frequency of injections for prophylaxis should be based on clinical response and adapted to each individual. *Glanzmann's thrombasthenia:* The recommended dose is 90 µg (range 80–120 µg) per kg body weight at intervals of two hours (1.5–2.5 hours). At least three doses should be administered to secure effective haemostasis. The recommended route of administration is bolu injection as lack of efficacy may appear in connection with continuous infusion. For those patients who are not refractory, platelets are the first line treatment for Glanzmann's thrombasthenia. *Severe postpartum haemorrhage:* In the management of severe postpartum haemorrhage, appropriate multidisciplinary expertise should be consulted. Dose range and dose interval: the recommended dose range for the treatment of bleeding is 60–90 µg per kg body weight administered by intravenous bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on clinical response of the individual patient. It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.
Contraindications: Hypersensitivity to the active substance, or to any of the excipients, or to mouse, hamster or bovine protein.
Special warnings and precautions for use: In severe postpartum haemorrhage and pregnancy, the clinical conditions (delivery, severe haemorrhage, transfusion, DIC, surgery/invasive procedures and coagulopathy) are known contributing factors to the thromboembolic risk; and in particular venous thromboembolic risk associated with the administration of NovoSeven.
Interaction with other medicinal products and other forms of interaction: The risk of a potential interaction between NovoSeven® and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided. Antifibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Antifibrinolytics are also used to reduce blood loss in women with postpartum haemorrhage. Experience with concomitant administration of antifibrinolytics and rFVIIa treatment is however limited. Based on a non-clinical study it is not recommended to combine rFVIIa and rFXIII. There are no clinical data available on interaction between rFVIIa and rFXIII.

Please update this abbreviated summary of products characteristics with local product information

Fertility, pregnancy and breast-feeding: As a precautionary measure, it is preferable to avoid the use of NovoSeven® during pregnancy. Data from non-clinical studies as well as post-marketing data show no indication that NovoSeven® has a harmful effect on male or female fertility. Limited data from exposed pregnancies did not show any adverse effect on pregnancy or on the health of foetus/new-born child. It is unknown whether NovoSeven® is excreted in human breast milk.
Undesirable effects: The most frequent adverse drug reactions (ADR) are pyrexia and rash (uncommon: ≥ 1/1,000 to < 1/100), and the most serious adverse drug reactions include venous thromboembolic events (uncommon: ≥ 1/1,000 to < 1/100) and arterial thromboembolic events (rare: ≥ 1/10,000 to < 1/1,000). The frequencies of both serious and non-serious adverse drug reactions are listed by system organ class: Blood and lymphatic system disorders: *Rare:* Disseminated intravascular coagulation, related laboratory findings, including elevated levels of D- dimer and decreased levels of Anti Thrombin (AT) and coagulopathy. Gastrointestinal disorders: *Rare:* nausea. General disorders and administration site conditions: *Uncommon:* ADRs are decreased therapeutic response and pyrexia. *Rare:* ADR is injection site reaction including injection site pain. Immune system disorders: Hypersensitivity is *Rare*; anaphylactic reaction frequency is not known. Investigations: *Rare:* increased fibrin degradation products, increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Nervous system disorders: *Rare:* headache, skin and subcutaneous tissue disorders: *Uncommon:* Rash (including allergic dermatitis and rash erythematous), pruritus and urticaria. Unknown frequency: flushing and angioedema. Vascular disorders: *Uncommon:* venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia). *Rare:* Arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia), Angina pectoris. *Unknown:* Intracardiac thrombus.
Inhibitory antibodies: In post-marketing experience, there have been no reports of inhibitory antibodies against NovoSeven® or FVII in patients with haemophilia A or B. In factor VII deficiency clinical trials: formation of antibodies against NovoSeven® and FVII is the only ADR reported (common). Development of inhibitory antibodies to NovoSeven® has been reported in a post-marketing observational registry of patients with congenital FVII deficiency.
tions after authorisation of the medicinal product is im-
g of the benefit/risk balance of the medicinal product.
erdose have been reported in patients with haemophilia
ted in connection with an overdose was a slight transient
-old patient receiving 24 mg rFVIIa instead of 5.5 mg. No
in patients with acquired haemophilia or Glanzmann's
r VII deficiency, where the recommended dose is 15–30
has been associated with a thrombotic event (occipital stroke) in an elderly (> 80 year) male patient treated with 10–20 times the recommended dose. In addition, the development of antibodies against NovoSeven® and FVII has been associated with overdose in one patient with factor VII deficiency. The dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred.
Administration: NovoSeven® (eptacog alfa activated) is administered intravenously over 2–5 minutes.
Caution: Some needleless connectors with an internal spike used with central venous access devices (CVADs) may be incompatible with the pre-filled glass syringe and prevent administration. Therefore, use of an alternative sterile 10ml luer-lock plastic syringe may be required for withdrawal and injection of the reconstituted solution. Follow the instructions for use for the CVAD and needleless connector.
Storage and shelf life: The shelf life for the product packed for sale is 3 years when the product is stored below 25°C.
In vial: After reconstitution, chemical and physical stability has been demonstrated for 6 hours at 25°C and 24 hours at 5°C. From a microbiological point of view, the product should be used immediately. If not used immediately, storage time and storage conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C–8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. The reconstituted solution should be stored in the vial.
In syringe (50 ml polypropylene) in hospital settings only: Reconstitution must take place in controlled and validated aseptic conditions by adequately trained staff. Under these conditions, chemical and physical stability has been demonstrated for 24 hours at 25°C when stored in a 50 ml syringe (polypropylene). If not used immediately, the conditions prior to use are the responsibility of the user and the in-use storage time must not be longer than as stated above.
Procedure for pooling of vials for hospital use only: During in vitro studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 25°C in a 50 ml syringe (polypropylene). Compatibility with the product was demonstrated for the system consisting of a 50 ml syringe (polypropylene), a 2 m infusion tube (polyethylene) and an in-line filter with a 5 micrometer pore size. The syringe with adequately reconstituted product can be used for administration in a CE- marked infusion pump (accepting a 50 ml syringe), for details on pooling the vials (hospital use only) please refer to the SmPC as of May 2022. The infusion pump must only be operated by trained hospital personnel.
Legal category: Prescription-only medicine (POM). MARKETING AUTHORISATION NUMBERS: NovoSeven 1 mg (50 KIU): EU/1/96/006/008. NovoSeven 2 mg (100 KIU): EU/1/96/006/009. NovoSeven 5 mg (250 KIU): EU/1/96/006/010. NovoSeven 8 mg (400 KIU): EU/1/96/006/011. **Authorisation holder:** Novo Nordisk A/S, Bagsvaerd, Denmark. **Date of last revision *SMPC*:** May 2022. **For more detailed information please consult the EMEA product information.** Novo Nordisk® is a registered trademark owned by Novo Nordisk A/S. NovoSeven® is a registered trademark owned by Novo Nordisk Health Care AG, The Circle 32/38, 8058 Zürich, Switzerland, Tel +41432224300. **Veeva ID:** HQ22NS00030

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